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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,715	02/13/2002	Michael Chopp	1059.00073	9739

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1614	

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03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/075,715	CHOPP ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/26/07 has been entered.

The response filed 12**/26/07** presents remarks and arguments to the office action mailed **10/4/07**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration

The Declaration of Dr. Michael Chopp submitted on 12/26/07 is acknowledged and has been reviewed. The declaration supports evidence of only PDE5, there are

wide variations of PDE, Applicant has not shown that other PDE's are capable of performing the same.

Status of claims

Claims 1, 6-8 and 14-17 are pending in this application. Claims 2-5 and 9-13 are cancelled. Claims 1, 6-8 are amended and claims 14-17 are newly submitted.

Maintained *Claim Rejections - 35 USC § 112*

Applicant argues that all PDE5 as well as all known and that statins induce cGMP, however the affidavit only narrows it to PDE5 inhibitors.

In response, the claims recite phosphodiesterase and not phosphodiesterase 5 inhibitors. This also applies to the statins, only two statins are shown. The rejection is maintained for this reason because the declaration does not overcome the written description because testing does not provide written description.

Claims 1, 6-8 and 14-17 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant has not provided a description of the structures of a representative number of compounds, nor a description of the chemical and/or physical characteristics of a representative number of compounds, nor a description of how to obtain a representative number of specific compounds.

In other words, the Applicant has not described with sufficient clarity what these statins and phophodiesterase inhibitors are contemplated. The claims encompass any statin or phosphodiesterase known and unknown. A cursory examination of statins and or phosphodiesterase, for example, in related publications within the scientific literature indicates the existence of a very wide array of compounds. No distinguishing features by members of those broad genera have been provided in the instant disclosure. The scope of the claims extends to numerous structural variants, and the genera are highly variable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Quast et al., Brain research 677(20 1995, 204-212 taken with Horackova et al. Am. J. Physiol. Cell 269(2) Abstract only, 1995 in view of Cooke et al. US 5,428,070.

Quast et al. teach administering L-arginine (as N-monomethyl-L-arginine) to rats after ischemic stroke has occurred. See underlining pages 204, 205 and 209. The reference fails to teach identifying new neuron growth as required by the instant claim.

Horackova et al. teach more nitric oxide synthesizing neurons are present after the administration of a nitric oxide donor S—nitroso-N-acetylpenicillinamine implying new neurons are made thus the interpretation of more. See underlining abstract. The reference suggest SNAP augument neurons. See underlining. Although Horackova did not use the L-arginine , SNAP is a nitric oxide donor, therefore substituting one for another is within the purview of one of ordinary skill in the art because both ar know nitric oxide donors and would expect to function the same.

Cooke et al. teach administering L-arginine (see col. 3, lines 54-57) after vascular injury with emphasis on decreasing the effects of atherogenesis. (please note that atherosclerotic vascular diseases such as stroke is higher in patients with non–insulin-dependent diabetes mellitus) wherein the conditions may result in stroke. See col. 1, lines 33-48. The drug L-arginine is administered after the injury (post). See col. 3, lines 52-55 and cGMP is increased (see col. 9, lines 22-24) resulting in new neuron growth.

One of ordinary skill in the art would have been motivated to administer L-arginine to patients post stroke in order to promote neurogenesis, or growth of new

neurons, because *L*-arginine is the substrate for nitric oxide (NO) production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. And as shown increase in cGMP was achieved by administration of L-arginine, see col. 9, lines 22-24.

It would have been obvious to one of ordinary skill in the art to combine the above cited references and administer L-arginine in a post stroke event to a patient because the art teaches so and with regards to identifying increased numbers of new neurons, the teaching of Horackova indicates that more neurons are present since L-arginine increases the beating of myocytes see underlying.
Therefore it would have been obvious to have affected new neuron growth in a patient by administering in a post ischemic event L-arginine from the teachings of the cited references above.

Claims 1 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooke et al., US 5,428,070 taken with Liao, US 6,423,751, in view of Kaposzta, (*Circulation*. 2001;103:2371-2375) taken with Ohtsuka et al., The American J. of Med. Vol. 108, (5) 2000, 439 (of record) further in view of (newly applied) Quast et al., Brain research 677(20 1995, 204-212 taken with Horackova et al. Am. J. Physiol. Cell 269(2) Abstract only, 1995.

Cooke is applied as above.

Liao teaches up-regulation of endothelial cell nitric oxide synthase expression (col. 3, lines 24-31) by administration of HMG-Co reductase inhibitors for example atorvastatin, fluvastatin, cerivastatin (all statins) for the treatment of stroke (patients

having experience stroke, see col. 9, lines 20-30. Liao teaches a surprising connection was made in the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. See col. 8, lines 59-65.

Kaposta teaches the administration of L-arginine in combination with S-nitrglutathione (a nitric oxide donor) in the treatment of postoperative stroke risk. See page, 2371 background section. One of ordinary skill in the art would have been motivated to replace the S-nitrglutathione with L-arginine as both are NO-donors and expect the same result with the use of L-arginine as the functions and activation would be the same.

Ohtsuka et al. teach cognitive functions increased with the administration of L-arginine (see report). It is Examiners understanding that since cognitive function is increased, the replacement of old or dead neurons with newly forms attributes to that absent factual evidence.

Quast and Horackova are applied here as above.

Combination the cited references would have been obvious to one of ordinary skill in the art to treat post-stroke patients. By administering L-arginine, cGMP is increased. One of ordinary skill in the art would have been motivated to combine the prior art references and administer L-arginine to post-stroke patients in order to increase neurological function, such as cognition, because the references teach or suggest so. There are only two ways growth can occur: by either producing new neurons to replace

the old or regeneration of old neurons, which is within the knowledge of one of ordinary skill in the art.

MPEP 2112.01"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not."

Nothing unobvious is seen in combining said cited art as they teach administering the same compounds (L-arginine, Statins) for the same type of disease (treating post-stroke). Also, with regards to increasing neurological function as stated by MPEP it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full para.).

The claimed invention was prima facie obvious to make and use at the time it was made.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liao, US 6,423,751 (of record).

Liao teaches up-regulation of endothelial cell nitric oxide synthase expression (col. 3, lines 24-31) by administration of HMG-Co reductase inhibitors for example atorvastatin, fluvastatin, cerivastatin (all statins) for the treatment of stroke (patients having experience stroke, see col. 9, lines 20-30. Liao teaches a surprising connection was made in the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. See col. 8, lines 59-65.

The reference fails to teach neuron growth and identifying increased numbers of new neurons.

However, based upon the teaching from the background section indicating that in mammals nitric oxide are expressed in neurons of nitric oxide synthase and are expressed in endothelial cells nitric oxide synthase. Thus from the knowledge of one of ordinary skill in the art that nitric oxide is responsible for neurogenesis, meaningly neurogenesis support new growth or augument to old to proliferate.
Therefore one of ordinary skill in the art would be motivated to increase nitric oxide either by administering a nitric oxide donor directly or through nitric.

Also, with regards to increasing neurological function and cognitive in a patient as stated by MPEP it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205

USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full para.).

Maintained Double Patenting (No arguments to this rejection are noted)

Claim **1, 6 – 8 and 14-17** remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-13** of U.S. Patent Application No. **10,500,694**. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to treating neurological functions resulting from stroke, in the current application (claims **1, 6-8 and 14-17**), and neurological functions in general (claims 1 -13) in the copending application. The current application claims are obvious variation of the copending application claims

Both applications recite using the same compositions and/or derivatives thereof. See current application claims **1, 6-8 and 14-17**, wherein the compounds are selected from L-arginine, sildenafil, statins and phosphodiesterase inhibitors, and in the copending application claims 1-13 the, compound is selected from phosphodiesterase inhibitors. The compositions recited in the claims are obvious of each other.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

No claim is allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG

March 15, 2008

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614